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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/590,991	06/09/2000	John E. Adamou	469201-475	2154

7590 10/23/2003

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ART UNIT	**PAPER NUMBER**
1645	18

DATE MAILED: 10/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/590,991	ADAMOU ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-15 and 17-32* is/are pending in the application.

4a) Of the above claim(s) *5-15, 17-22 and 25-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 04/28/03 (paper no. 16) has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 04/28/03 (paper no. 17) in response to the final Office Action mailed 08/28/02 (paper no. 9).

Status of Claims

3) Claim 1 has been amended via the amendment filed 04/28/03.

Claims 1, 4-15 and 17-32 are pending.

Claims 1, 4, 23 and 24 are under examination.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' information disclosure statement filed 06/09/03 (paper no. 15). The information referred to therein has been considered and an initialed copy is attached to this Office Action (paper no. 18).

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

7) The objection to the drawings made in paragraph 3 of the Office Action mailed 12/21/01 (paper no. 6) is withdrawn in light of Applicants' submission of formal drawings. These drawings have been approved by the Draftsperson.

Rejection(s) Withdrawn

8) The rejection of claims 1 and 23 made in paragraph 6 of the Office Action mailed 12/21/01 (paper no. 6) and made/maintained in paragraphs 19 and 20 of the Office Action mailed 08/28/02 (paper no. 9) under 35 U.S.C. § 112, first paragraph, as being non-enabled, is withdrawn in light of Applicants' amendments to the claims.

9) The rejection of claims 1 and 4 made in paragraph 21 of the Office Action mailed 08/28/02 (paper no. 9) under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendments to the claims.

10) The rejection of claims 23 and 24 made in paragraph 22 of the Office Action mailed 08/28/02 (paper no. 9) under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendments to the claims.

11) The rejection of claim 1 made in paragraph 23(a) of the Office Action mailed 08/28/02 (paper no. 9) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claim.

12) The rejection of claim 4 made in paragraph 23(b) of the Office Action mailed 08/28/02 (paper no. 9) under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the base claim.

Rejection(s) Maintained

13) The rejection of claim 23 made in paragraph 23(a) and the rejection of the dependent claim 24 in paragraph 23(b) of the Office Action mailed 08/28/02 (paper no. 9) under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein. Claim 23 still includes the recitation 'identical to SEQ ID NO: 6' without particularly reciting that the SEQ ID NO: 6 represents an amino acid sequence.

Rejection(s) under 35 U.S.C § 112, First Paragraph

14) Claims 1 and 23 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It is noted that the polypeptide recited in the claims does not exist independent of its function,

i.e., ability to elicit antibodies 'against *Streptococcus pneumoniae*', i.e., *Streptococcus pneumoniae*-specific antibodies, or the ability to 'bind to antibodies against *Streptococcus pneumoniae*' when administered to an animal. The specification discloses therapeutic or prophylactic applications and screening (antigenic) intentions for the claimed polypeptide variant. However, the instant specification fails to teach a single variant of a polypeptide sequence having at least 95% identity to the amino acid sequence of SEQ ID NO: 6 and concurrently having the ability to elicit antibodies 'against *Streptococcus pneumoniae*', i.e., *Streptococcus pneumoniae*-specific antibodies, or the ability to bind antibodies 'against *Streptococcus pneumoniae*'. Screening applications require at least a specific interaction of the polypeptide with a specific binding partner. Vaccine or therapeutic applications minimally require induction of native polypeptide-specific antibodies that at least bind specifically to the infecting *Streptococcus pneumoniae*. The precise structure or relevant identifying characteristics of each DNA molecule that encodes a variant polypeptide having at least 95% identity to the native amino acid sequence of SEQ ID NO: 6 and the ability to elicit antibodies 'against *Streptococcus pneumoniae*', i.e., *Streptococcus pneumoniae*-specific antibodies, or the ability to bind specifically to 'antibodies against *Streptococcus pneumoniae*' when administered to any animal can only be determined empirically by actually making every DNA molecule that encodes the polypeptide of the recited variability, i.e., the instantly recited 95% sequence identity, and testing each varied DNA molecule to determine whether it encodes the 95% modified polypeptide variant having the particularly disclosed functional or biologic activity. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement that the invention includes a polypeptide having at least 95% identity to the amino acid sequence of SEQ ID NO: 6 is insufficient to meet the adequate written description requirement under 35 U.S.C. § 112, first paragraph. The polypeptide of SEQ ID NO: 6 has specific biologic properties dictated by the structure of the polypeptide and the corresponding structure of the structural gene sequence which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the polypeptide encoded, and the function of the encoded polypeptide. The function cannot be predicted from the modification of the

structure of the gene and in the instant case, the DNA encoding the at least 95% modified polypeptide variant. Applicants have not shown that variation or modification of a reference sequence encoding a reference polypeptide as claimed, would automatically predict the production of a polypeptide variant having the recited functional activity, i.e., ability to elicit antibodies 'against *Streptococcus pneumoniae*', i.e., *Streptococcus pneumoniae*-specific antibodies, and the ability to bind to 'antibodies against *Streptococcus pneumoniae*'. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of DNA molecules encoding a representative number of species of polypeptide variants of at least 95% sequence identity as recited, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. With the exception of a polypeptide of SEQ ID NO: 6, a skilled artisan cannot envision the detailed chemical structure of all the polypeptide variant species encompassed by the recited molecule. *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111* states that Applicant "must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, is for purposes of the 'written description' inquiry, whatever is now claimed." See page 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." See page 1116 of *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111.* Applicants should also note that *Vas-Cath Inc. V. Mathukar, 19 USPQ2d 1111* makes clear that the written description provision of 35 U.S.C § 112, first paragraph, is severable from its enablement provision. See page 1115. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that its is a part of the invention and a reference to a potential method of isolating it. The nucleic acid encoding the claimed polypeptide variant having the required biologic function(s) itself is required. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.*

15) (a) Claims 1 and 23 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 6 which elicits antibodies specific to the polypeptide when administered to a mammalian animal, does not reasonably provide enablement for a polypeptide having 95% identity to

the amino acid sequence of SEQ ID NO: 6 that is capable of eliciting antibodies against '*Streptococcus pneumoniae*', i.e., against homologous or heterologous strains or serotypes of *Streptococcus pneumoniae*, as claimed in a generic sense, or for a polypeptide having 95% identity to the amino acid sequence of SEQ ID NO: 6 that binds to antibodies against the generically recited '*Streptococcus pneumoniae*', when administered to an animal.

(b) Claims 4 and 24 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 6 which elicits antibodies specific to the polypeptide when administered to a mammalian animal, does not reasonably provide enablement for such a polypeptide that is capable of eliciting 'protective' antibodies against homologous or any heterologous strain or serotype of *Streptococcus pneumoniae*, as claimed, other than against a specific strain of serotype 6B *S. pneumoniae*, strain SJ2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the polypeptide having at least 95% identity to the amino acid sequence of SEQ ID NO: 6, i.e., the polypeptide variant, is recited as being effective in eliciting antibodies 'against *Streptococcus pneumoniae*', or as being able to bind to antibodies 'against *Streptococcus pneumoniae*' when administered to an animal. This polypeptide variant is thus required to serve as an immunogenic or antigenic composition, or as a vaccine. In other words, the recited polypeptide variant having at least 5% dissimilarity with the amino acid sequence of SEQ ID NO: 6 is *required* to

have the ability to elicit antibodies 'against *Streptococcus pneumoniae*', and is *required* to have the ability to bind to antibodies 'against *Streptococcus pneumoniae*' when administered to an animal. However, the precise structural composition of a polypeptide having at least 95% continuous or discontinuous sequence identity with the polypeptide of SEQ ID NO: 6 and concurrently having the recited functional activities, is not disclosed. Applicants point to lines 1-5 and 24-28 on page 13 of the specification for the recitation '95% identical'. However, a mere recitation of such a phrase does not provide enabling disclosure for a polypeptide variant having 95% sequence identity to the polypeptide of SEQ ID NO: 6 and the requisite functions. The instant specification does not teach how to make a polypeptide of the amino acid sequence SEQ ID NO: 6 with 5% of its amino acids varied or modified in such a way that the resultant polypeptide variant still maintains the specific *Streptococcus pneumoniae*-binding ability, or specific immunogenic integrity. Neither the specification nor the art discloses a polypeptide variant that is at least 5% non-identical to the amino acid sequence of SEQ ID NO: 6 which variant retains the ability to elicit *Streptococcus pneumoniae*-specific antibodies. The instant specification fails to demonstrate that a polypeptide variant having at least 95% identity to SEQ ID NO: 6, if prepared by one of skill in the art, would retain all the functional or biological properties of the native polypeptide of SEQ ID NO: 6. It should be noted that predictability or unpredictability is one of the *Wands* factors for enablement. The precise structural composition of the claimed polypeptide variant is not disclosed, without which one of ordinary skill in the art cannot make and use the claimed product for the intended purpose(s), without undue experimentation. The specification lacks disclosure as to how to produce a polypeptide variant having at least 95% sequence identity to SEQ ID NO: 6 and at the same time having all the necessary or recited functions for use as a vaccine, an immunogenic composition, or an antigenic composition. This is critical because the art reflects sensitivity of proteins or polypeptides to alteration of even a single amino acid residue in its amino acid sequence. An alteration in a single amino acid can eliminate or drastically change one or more function(s) of the polypeptide. For instance, Bowie *et al.* (*Science* 247: 1306-1310, 1990, already of record) taught that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie *et al.* further taught that the problem of

predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (see column 1 on page 1306). taught that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function(s) is limited. Certain positions in the polypeptide sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (see column 2 on page 1306). Burgess *et al* (*J. Cell Biol.* 111: 2129-2138, 1990, already of record) taught that replacement of a single lysine residue at position 118 of the protein, acidic fibroblast growth factor, by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similar teachings are provided by Lazar *et al* (*Mol. Cellular Biol.* 8: 1247-1252, 1988, already of record) who showed that in the protein, transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity, while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. In the instant case, it is unlikely that a polypeptide molecule having as much as 5% dissimilarity with the native polypeptide of SEQ ID NO: 6 as recited, would have its primary, secondary or tertiary structure unchanged and would have the functional activity retained. The effects of such a high dissimilarity upon the polypeptide structure and function are unpredictable. One of skill in the art cannot predict that such a polypeptide variant would have its immunologic or biologic specificity protected or retained. Thus, while the art demonstrates that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein or polypeptide, with as much as 5% dissimilarity to the polypeptide of SEQ ID NO: 6, the specific binding or specific immunogenic activities of the claimed polypeptide variant could not be predicted, based solely on the sequence identity, nor would it be expected to be the same as that of the native polypeptide of SEQ ID NO: 6. For example, if one nucleotide in the nucleotide sequence that encodes the polypeptide of SEQ ID NO: 6 is deleted or inserted at a single position within the coding sequence, all the codons down stream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the polypeptide expressed will have little in common structurally or functionally with the native polypeptide of SEQ ID NO: 6. There is no certainty that

amino acid substitutions at any position would yield a polypeptide variant that retains the function and/or the specificity of the native polypeptide of SEQ ID NO: 6. The specification fails to demonstrate that a polypeptide having at least 5% structural dissimilarity to the polypeptide of SEQ ID NO: 6 would be functionally equivalent to the native polypeptide of SEQ ID NO: 6, particularly with regard to the specific binding ability and the ability to elicit protective antibodies 'against *Streptococcus pneumoniae*', i.e., any strain or serotype of *Streptococcus pneumoniae*. One simply cannot predict what effects a given deletion, insertion or modification in the amino acid sequence would cause, and therefore such modified molecules are not enabled as Applicants' invention. Applicants have not enabled the full scope of the invention as claimed for those polypeptide molecules which are altered or varied. The specification only discloses a functional polypeptide of SEQ ID NO: 6 and its ability to induce antibodies specific to the polypeptide. Furthermore, there is no showing that every serotype or strain of *Streptococcus pneumoniae* produces the polypeptide having the structure of SEQ ID NO: 6, or a structure that is 95% identical to SEQ ID NO: 6. Therefore, there is no predictability that the antibodies elicited by the polypeptide having the structure of SEQ ID NO: 6, or a polypeptide structure that is 95% identical to SEQ ID NO: 6 would be specific to, would bind to, or would be protective 'against' any *Streptococcus pneumoniae*, as recited generically. Undisclosed and unidentified functional polypeptide molecules of at least 95% identity encompassed in the claims are not enabled for their scope. Although a skilled artisan might envision making a number of changes in the reference polynucleotide sequence encoding the polypeptide in accordance with Applicants' disclosure, it is highly uncertain that the resultant polypeptide variant would be functionally equivalent to the native polypeptide of SEQ ID NO: 6. The altered polypeptide would vary in an unknown or unpredictable manner from the disclosed native polypeptide sequence. For these reasons, making and using of the instantly claimed polypeptide variant having the desired function(s) is well outside the realm of routine experimentation.

The retention of the immunologic specificity following one or more amino acid substitutions or deletions in a microbial polypeptide is another factor that has been shown to be unpredictable in the art. For instance, McGuinnes *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993) taught that "[a] single amino acid change within an epitope, or an amino acid deletion outside an epitope, were both

associated with loss of subtype specificity resulting from a change in the predicted conformation at the apex of the loop structure" in case of a meningococcal polypeptide (see abstract). Similarly, McGuinnes *et al.* (*Lancet* 337: 514-517, March 1991) taught that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 resulted in "striking changes in the structural and immunological properties of the class 1 protein" of this isolate (see abstract and page 514). These prior art references also demonstrated the unpredictability in obtaining a 'functional' variant of a microbial polypeptide. Therefore, absent a concrete showing, it is not predictable that a vaccine or an immunogenic composition comprising a polypeptide of the recited percent identity, would have the ability to induce a *Streptococcus pneumoniae*-specific protective antibodies against any strain or serotype of *Streptococcus pneumoniae*. The specification provides no guidance as to which specific amino acids must be retained or which may be varied or substituted without causing any detrimental effect to the claimed polypeptide that is required to induce 'protective' antibodies, or *Streptococcus pneumoniae*-specific antibodies in an animal against any isolate, strain or serotype of *Streptococcus pneumoniae*. There is no disclosure in the instant specification with regard to which amino acid variations, i.e., insertions, deletions, additions and substitutions, in the polypeptide would result in a polypeptide having 95% continuous or discontinuous sequence homology that would concurrently retain the functional integrity or biological/immunogenic competence of the native polypeptide, without rendering it non-functional. While the art has established that a single amino acid substitution can render a polypeptide non-functional, it is unlikely that a polypeptide having 95% continuous or discontinuous sequence homology to SEQ ID NO: 6 would retain the function of inducing *Streptococcus pneumoniae*-specific antibodies in an unspecified animal, absent evidence to the contrary. Although a microbial polypeptide having at least 5% dissimilarity with the native polypeptide is expected in the art to generally induce some antibodies, the specificity of such antibodies to the native polypeptide, or to *Streptococcus pneumoniae*, that too any strain, serotype or isolate of *Streptococcus pneumoniae*, is simply not predictable. This is important because the art reflects unpredictability as to which amino acids in a specific protein can be varied, i.e., replaced or added, without adversely affecting the functional properties of that specific protein. While it is known in the art that variation in one or more amino acids is possible in a given protein, the exact

position within its amino acid sequence where replacements or variations can be made, with a reasonable expectation of success of retaining the protein's functional integrity, is not certain. A random replacement affecting the epitopic amino acid positions that are critical, for example, to the three-dimensional conformational structure and specific binding property of the protein, would result in a polypeptide that may be non-functional (i.e., non-immunogenic) or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool.

Thus, the art reflects that variations in critical residues at specific positions in an amino acid sequence could result in a polypeptide which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. In the instant case, this is important because the purpose of the instant invention is to induce an immune response that is specifically protective 'against' any strain, isolate or serotype of *Streptococcus pneumoniae,* or antibodies that specifically bind to any strain, isolate or serotype of *Streptococcus pneumoniae* in any animal, including humans. Absent a concrete demonstration, the genus-specificity of a single microbial polypeptide or its variant is not predictable, since it is well known in the art that some microbial polypeptides are genus specific, while others show heterogeneity and remain serotype- or strain-specific. The claims are viewed as being non-enabled with regard to their full scope. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as reflected in the state of the art, the art-demonstrated unpredictability in determining amino acid variations that are acceptable, and the quantity of experimentation necessary. *Ex parte Foreman, 230 USPQ 546, 547 (Bd. Pat. Appls. And Interf. 1986)*. Examples demonstrating the specific binding of the claimed polypeptide or its variant to antibodies raised against a representative number of strains or serotypes

of *Streptococcus pneumoniae*, and providing protection against a representative number of strains or serotypes of *Streptococcus pneumoniae* are lacking in the instant specification. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph. In this regard, it should be noted that the courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. See *Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001)*. Moreover, the specification must have been enabling at the time the invention was made (see *In re Wright, 27 USPQ2d 1510*).

16) Claim 4 is rejected under 35 U.S.C. § 112, first paragraph, because the specification while being enabling for an immunogenic composition containing a serotype 4 (Norway strain) *S. pneumoniae* polypeptide comprising the amino acid sequence of SEQ ID NO: 6 and a pharmaceutically acceptable carrier, wherein the polypeptide is present in an amount effective to elicit protective antibodies in a mammalian animal against challenge with a serotype 6B of *S. pneumoniae,* does not reasonably provide enablement for such a composition wherein the polypeptide is effective to elicit protective antibodies in any animal against challenge with any serotype of *S. pneumoniae* other than serotype 6B, or any strain of *S. pneumoniae*.

In the instant case, the scope of the claim broadly encompasses a composition comprising a polypeptide of the amino acid sequence of SEQ ID NO: 6 which is effective in eliciting protective antibodies in any animal, mammalian or non-mammalian, human or non-human, against any serotype of *S. pneumoniae*, or any strain of *S. pneumoniae*, including the one that does not produce the polypeptide of SEQ ID NO: 6. However, the instant specification does not teach a composition of such a broad scope. The instant specification, for example at Figure 1, teaches an immunogenic composition comprising an effective amount of a polypeptide having an amino acid sequence that is 100% identical to SEQ ID NO: 6 from serotype 4 (Norway strain) *S. pneumoniae* and a pharmaceutically acceptable carrier, wherein the polypeptide elicits protective antibodies in a mammalian animal against challenge with serotype 6B *S. pneumoniae,* strain SJ2. The limitation 'animal' encompasses an animal that is vertebrate, non-vertebrate, mammalian, non-mammalian, multicellular, transgenic etc., The limitation, '*Streptococcus pneumoniae*', encompasses multiple serotypes of *Streptococcus pneumoniae,* including the 23 serotypes of *S. pneumoniae*. However,

there is no evidence in the instant specification showing that one or more polypeptide variants of SEQ ID NO: 6, obtained from serotype 4 of *S. pneumoniae*, or a non-serotype 4 *S. pneumoniae*, would indeed elicit "protective" antibodies in any animal against any species of the genus *Streptococcus* other than *S. pneumoniae*, or any serotype of *S. pneumoniae* other than serotype 6B. There is no showing that the claimed polypeptide variants are immunologically or biologically effective against all species of the genus *Streptococcus*, or all serotypes of *S. pneumoniae*. This is important because the ability of a microbial polypeptide or its variants to confer broad genus-wide, species-wide or serotype-wide protection is not predictable. There is no evidence that the polypeptide of SEQ ID NO: 6 is produced by all members or species of the genus *Streptococcus*, or by all serotypes of *S. pneumoniae* other than serotype 4. The evidence is clearly not commensurate in scope with the breadth of the claim. Absent concrete evidence showing that the claimed polypeptide (or its variant as claimed) is produced by all serotypes of *Streptococcus pneumoniae* and that it confers homologous and heterologous protection against any serotype of *S. pneumoniae* other than 6B, claim 4 is viewed as being non-enabled with respect to its full scope. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claim.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

17) Claim 1 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The amended claim 1 now includes the limitations: 'immunogenic composition' comprising a polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID N: 6 and present in a carrier in an amount effective to elicit production of antibodies against *Streptococcus pneumoniae* 'when administered to an animal'. Applicants point to page 13, lines 1-5 and 24-28 of the specification as providing support for the added limitation. This part of the specification describes immunogenic fragments comprising an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 6. However, there is no descriptive support in these parts of the specification for a such a polypeptide variant or fragment having the recited

function, i.e., the ability to elicit 'antibodies against *Streptococcus pneumoniae* when administered to an animal'. A composition comprising such a polypeptide variant has not been administered to any animal. Therefore, the above-identified new limitations in claim 1 are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or to remove the new matter from the claim(s).

18) Claim 23 is rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 23 includes the limitations: polypeptide comprising an amino acid sequence at least 95% identical to SEQ ID N: 6 wherein said polypeptide 'binds to' antibodies against *Streptococcus pneumoniae* when administered to an animal. Applicants point to page 13, lines 1-5 of the specification as providing descriptive support for the limitation. However, there appears to be no descriptive support in this part of the specification for a polypeptide comprising an amino acid sequence 95% identical to SEQ ID N: 6 wherein the polypeptide 'binds to antibodies against *Streptococcus pneumoniae* when administered to an animal'. A polypeptide with 95% identity to the amino acid sequence of SEQ ID NO: 6 which has the functional ability to bind to antibodies against *Streptococcus pneumoniae* when administered to an animal is not described within the instant specification, as originally filed. Such a polypeptide variant has not been administered to any animal. Therefore, the above-identified limitations in claim 23 are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the new limitation(s), or to remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

19) Claims 1, 4, 23 and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and confusing in the recitation "composition comprising a polypeptide ..... and present in a carrier in an amount effective to elicit production of antibodies....". For clarity and in order to distinctly claim the subject matter, it is suggested that Applicants replace the phrase with: --composition comprising a polypeptide ..... and a carrier in an amount effective to elicit antibodies ...--.

(b) Analogous criticism applies to claim 4.

(c) Claim 23 is vague and indefinite in the recitation: 'binds to antibodies against *Streptococcus pneumoniae* when administered to an animal'. It is unclear how the claimed polypeptide variant can bind to antibodies against *Streptococcus pneumoniae* 'when administered to an animal'. It appears that for such a binding to take place, the 'antibodies against *Streptococcus pneumoniae*' have to be pre-existing, at the site of administration, in the animal to which the polypeptide is administered. Does it mean that if the polypeptide is administered intramuscularly with the 95% varied polypeptide of SEQ ID NO: 6, the injected polypeptide variant binds to antibodies against *Streptococcus pneumoniae* at the site of intramuscular injection? Clarification is requested.

(d) Claims 4 and 24, which depend from claims 1 and 23 respectively, are also rejected as being indefinite because of the vagueness identified above in the base claim(s).

Rejection(s) under 35 U.S.C. § 102

20) Claims 1, 4, 23 and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Kunsch *et al.* (WO 98/18930, already of record).

Kunsch *et al.* disclose a polypeptide having an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 6. See the enclosed search report; Table 1 and pages 92 and 93 of Kunsch *et al.* A vaccine comprising the polypeptide or fragments thereof, together with a pharmaceutically acceptable carrier, diluent or excipient, wherein the polypeptide is present in an amount effective to elicit a protective immune response to members of the *Streptococcus* genus in an animal, is taught (see pages 4 and 5; and claims 11, 12 and 16).

Claims 1, 4, 23 and 24 are anticipated by Kunsch *et al.*

Remarks

21) Claims 1, 4, 23 and 24 stand rejected.

22) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

23) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 7.45 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

October, 2003

S. DEVI, PH.D.
PRIMARY EXAMINER